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Several Biomolecular Parameters as Prognostic, Therapeutic and Preventive Factors of Nasopharyngeal Carcinoma

Farhat Farhat*

Departement of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Sunatera Utara, Medan, North Sumatera, Indonesia

Abstract

Introduction: Polymorphism of the enzyme in metabolyzing carcinogen such as CYP2E1 and GSTs are the genetic factor contributing for NPC. NPC also is related with several proteins that induce the growth and progression of tumor. Identification of the genetic variation and protein are beneficial for clinical use.
Review: CYP2E1 polymorphisms are associated with increased activity and enzyme transcription, thereby increasing the activation of nitrosamines as carcinogens in NPC. In addition, polymorphism of GSTs as the phase II enzyme decrease the act to detoxify carcinogen and inhibit oxidative stress. Several studies showed the relation of those polymorphism with the risk factor of NPC. The protein expression in NPC was also studied by several researchers. Several proteins in NPC such as p38 MPAK, TNF-α, NF- κB, PPAR-gamma, LMP-1, VEGF, COX-2, and MMP-9 are related with tumor growth, prognosis and also help in treatment of NPC.
Conclusion: Identifying GSTs and CYP2E1 polymorphism may be help in determining risk factor for NPC due to the association of those with increased susceptibility for NPC. Analyzing the protein expression by immunohistochemistry also help the clinician to identify the prognosis and considering therapy for NPC.

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Corresponding author:
Address: Jl. Dr. Mansyur No.5, Padang Bulan, Kec. Medan Baru, Kota Medan, Sumatera Utara 20155, Indonesia

e-mail: farhat@usu.ac.id

1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a unique malignancy due to its clear geographic distribution [1, 2]. The incidence of NPC is high in South China, Southeast Asia, North Africa and Arctic and the disease is rare in another parts of the world [3]. In Indonesia, the incidence of NPC are 8.3/100.000 for men and 3.0/100.000 for women [4]. NPC cases in Indonesia was about 12,000 cases per year [5]. The mortality of this malignancy is high because of the late diagnosis [6, 7]. The incidence of NPC in man is 2.3 fold higher than woman [8]. The average age of NPC patients is 50 years old [3].

Nasopharyngeal carcinoma is caused by the relation of several factors including genetic, Epstein-barr Virus infection (EBV), and environment. Several genetic factors have role in NPC development such as Human Leukocyte Antigen-A2 (HLA-A2), chromosome 3p deletion and polymorphism of enzyme in carcinogen metabolism including cytochrome P450 2E1 (CYP2E1) (9). Study showed that there was expression of latent EBV such as Epstein Barr Virus Nuclear Antigen (EBNA), Latent Membrane Protein-1 (LMP-1), LMP-2, and EBV Encoded Small RNAs (EBER) in NPC. Almost 90% of NPC with poor differentiation are positive for EBV serology test [9]. Environmental factors which are responsible in NPC are geographic location, race or ethnic, and food such as salted fish and preserved food. Other factors including smoking, dust or combustion residue, chemical substances such as formaldehyde are also thought to be related with NPC [9, 10].

Recent years, the therapy for NPC are directed to targeted therapy which inhibit the specific cancer pathways and molecule that are involved in the growth and progression of cancer. The example is cetuximab which is the monoclonal antibody for Epidermal Growth Factor Receptor (EGFR), the growth factor that has role in tumor growth. Studies show that administration of cetuximab in the treatment of NPC using carboplatin is more effective in recurrent or metastatic NPC that fail with platinum therapy [11]. Another therapy is beacizumab, which is a monoclonal antibody that specifically binds to and inhibits VEGF, thereby inhibiting tumor angiogenesis. Combination of beacizumab with chemotherapy agents increases the apoptotic chemotherapy action. This suggests a possible combination of targeted therapy with chemotherapy in the management of NPC [12]. Several other molecular therapies are gene therapy, immunotherapy and adoptive therapy [11]. Apart from helping in therapy, the use of biomarkers can be used as a prognostic factor for NPC. Patients with negative VEGF and JAK2 expressions showed a longer survival time than patients with positive VEGF and JAK2 expressions [13]. The biomarkers are the expressed protein and can be analyzed by immunohistochemistry.

2. MAIN TEXT

2.1 Genetic Polymorphism in NPC

Identification of gen in NPC provides an understanding of the molecular mechanisms of NPC. This is the basis for the discovery of biomarkers to assist in early diagnosis, therapy and prognosis of NPC [14, 15]. CYP2E1 is one of the genes that plays a role in the activation of pro-carcinogens such as nitrosamines found in cigarette smoke, salted fish and preserved food [14-16]. This enzyme polymorphism is associated with several cancers including NPC [16-18]. CYP2E1 polymorphisms are associated with increased activity and enzyme transcription, thereby increasing the activation of nitrosamines as carcinogens in NPC [9, 15, 16]. Study showed an increased risk of NPC associated with CYP2E1 polymorphisms. This risk is further increased when accompanied by exposure to carcinogens containing nitrosamines such as tobacco from cigarette smoke [19-21]. The importance of CYP2E1 inhibitors has been investigated in liver cancer. Chlormethiazole which is a CYP2E1 inhibitor has been found to work in reducing hepatocyte proliferation and hepatocarcinogenesis induced by nitrosamine [22]. Research on NPC may be conducted to determine the benefit of this therapy in nasopharyngeal carcinoma.

GSTs enzymes are enzymes that play a role in detoxifying carcinogens and inhibiting oxidative stress [23, 24]. Several types of GSTs enzymes include GSTA (α), GSTT1 (θ), GSTM1 (μ), GSTP1, GSTO1, GSTs and GSTZ1 (25). GSTM1 and GSTT1 are known to be associated with susceptibility to cancer. Deletions in genes, namely GSTM1 null and GSTT1 null cause loss of enzyme function in detoxifying carcinogens [26,

27]. Several studies have shown that the risk of developing NPC was higher in individuals with GSTM1 null or GSTT1 null [28, 29]. Apart from GSTM1 and GSTT1, the GSTP1 polymorphism namely Ile / Val GSTP1 is also associated with several cancers such as breast cancer, lung cancer and head and neck cancer [30, 31]. This polymorphism changes the binding site of the GSTP1 substrate, causing changes in the function of GSTP1 in detoxifying carcinogens that can promote cancer development. However, several studies found that there was no correlation between GSTP1 polymorphisms and NPC [28, 30]. GST enzyme polymorphisms also cause interference with the inhibition of oxidative stress caused by the accumulation of ROS [23]. Provision of antioxidants in cancer cases can be a consideration for NPC therapy based on the occurrence of oxidative stress. Studies show that there is an increase in superoxide dismutase, catalase, GST and glutathione reductase as an antioxidant enzyme and a decrease in DNA damage in a group of breast cancer patients with chemotherapy and intake of vitamin C and vitamin E supplements [32].

2.2 Protein Expression in NPC

Immunohistochemistry to detect protein expression has been performed in several studies to determine the diagnosis, prognosis and evaluation of cancer therapy, including NPC. The protein are:

2.2.1 p38 Mitogen-Activated Protein Kinase (p38 MAPK)

MAPK plays a role in cell growth including proliferation, differentiation and apoptosis of cells [33]. MAPK is associated with anti-apoptotic activation that causes cell transformation (34). Studies showed that there was a significant relationship between p38 MAPK expression and clinical stage in NPC [35]. The use of MAPK as a therapeutic target has been identified as a strategy against cancer [36]. The work of MAPK as a transcription regulator that functions through the control of gene expression as a process that often experiences dysfunction in disease makes MAPK a target therapy option [37]. A study of preclinical activity of the anticancer drug gefitinib in non-keratinized NPC showed suppression of epidermal growth factor induced by p-EGFR, p-MAPK, and p-STAT3 activation [38]. A PCR study on the MAPK pathway and the Aur-A protein showed that MAPK overexpression led to overexpression of Aur-A protein, which subsequently led to intracranial invasion and increased staging of NPC. [39].

2.2.2 Tumor Necrosis Factor-α (TNF-α)

TNF-α is known to be associated with malignancy and poor prognosis and cachexia. High levels of TNF-α are found in progressive NPC with an advanced rather than an early stage [40]. TNF-α can lead to increased tumor growth, stimulate the angiogenesis process, DNA damage and increase tumor metastasis potentiation in animal models [41]. TNF-α also increases tumor angiogenesis through several angiogenic factors such as interleukin-8 (IL-8) and Vascular Endothelial Growth Factor (VEGF) [42]. TNF-α overexpression is closely related to tumor recurrence and tumor spread to the lymph nodes [43]. Andersson et al found that TNF-α has high levels in advanced stages of head and neck cancer and was a potential biomarker for prognosis along with C-Reactive Protein (CRP) [44]. Study showed the potential of TNF-α monoclonal antibody as a good therapy in preventing the growth of NPC [45].

2.2.3 Nuclear Factor-Kappa B (NF-κB)

NF-κB in tumors play an active role in carcinogenesis through cell proliferation, cell apoptosis, inflammation and the immune system [46]. The roles of NF-κB in cell proliferation are activating cyclin D1 and c-myc expression, which are oncogens to induce cell proliferation. The targets of these transcription factors include TNF, Interleukin (IL) -8, and IL-1β which also work to stimulate cell proliferation [47]. NF-κB is also associated with cell invasion and tumor metastasis through induction of Epithelial-Mesenchymal Transition (EMT) [47].

NF-κB was found to be overexpressed in patients with NPC. The expression of these transcription factors is also associated with a poor prognosis for NPC [48]. The survival rate of patients with NF-κB expression was lower than without NF-κB expression [49]. Several targeted therapies for NF-κB include β-Hydroxyβ-methyl Butyrate (HMB), SPA3015 (P-glycoprotein (P-gp) analogue which inhibits the proliferative effect of NF-κB through inhibition of these transcription factors [50, 51].

2.2.4 Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-gamma)

PPAR-gamma has role in inflammation, glucose metabolism and cancer [52]. PPAR-gamma expression can inhibit cell proliferation and tumor growth, but can also stimulate proliferation in some cancer cells [52]. Studies show that PPAR-gamma can induce angiogenesis via VEGF stimulation in cancer cells [53]. PPAR-gamma expression is found in liposarcoma, breast cancer, colon cancer and prostate cancer [54].

PPAR-gamma expression is known to be associated with higher tumor staging and lower survival rates in patients with pancreatic carcinoma [55]. Study showed a significant reduction in the incidence of head and neck cancer in diabetes mellitus patients treated with thiazolidinedione which is a PPAR agonist [56]. However, there were studies that show the possibility of PPAR agonists in the induction of cancer such as pioglitazone which is associated with an increased risk of bladder cancer depending on the dose and duration of therapy [57].

2.2.5 Latent Membrane Protein-1 (LMP-1)

LMP-1 is expressed in about 65% of NPC. This protein is important in the formation of tumors associated with EBV infection [9]. LMP-1 is a proto-oncogen that is expressed by latent EBV infection [10, 58]. LMP-1 is known to activate several signaling pathways such as the signal pathways NF-κB, MAPK (Erk1 / 2, JNK. P38), STAT3, PI3-kinase/Akt, and others that play a role in the development of NPC (59, 60). LMP-1 are also involved in cell motility, cell invasion, cell proliferation and angiogenesis [61].

Rosales et al. demonstrated that LMP-1 expression was associated with parapharyngeal cavity invasion. This expression is thought to be associated with a poorer prognosis in patients with NPC [62]. A study by Yang et al showed that there was inhibition of cell proliferation in the therapy of NPC using DNAzymes. This therapy is a synthetic single-chain DNA catalyst that works through LMP-1 genetic manipulation. This agent causes decreased LMP-1 expression in NPC [63].

2.2.6 Vascular Endothelial Growth Factor (VEGF)

VEGF is known as a growth factor that plays a role in angiogenesis which is important in tumor growth, migration and endothelial proliferation [64]. VEGF is also known to be associated with tumor stage, lymph node involvement and metastases [65]. Study showed that NPC patients with VEGF overexpression have a poor prognosis compared to those without VEGF expression [66]. Dan et al. found that VEGF overexpression is an independent prognostic factor in NPC [67].

2.2.7 Cyclooxygenase-2 (COX-2)

COX-2 is involved in prostaglandin production, inflammation and cancer [68, 69]. COX-2 activity produces prostaglandin E2 (PGE2) products which cause carcinogenesis through cell protection against apoptosis, potentiation of cell proliferation, angiogenesis, invasive and metastatic [68, 69]. Study showed an association of COX-2 overexpression with low survival in patients with NPC (66). COX-2 overexpression is also associated with tumor size, lymph node involvement, clinical stage, distant metastases, tumor recurrence in patients with NPC [70, 71]. The majority of current studies focus on the prognostic value of COX-2 and the benefits of COX-2 inhibitors in cancer. COX-2 inhibitors in cancer therapy are generally associated with other factors such as Matrix Metalloproteinase (MMP) and TNF-α [72, 73].

2.2.8 Matriks Metalloproteinase-9 (MMP-9)

MMP-9 is an enzyme that is often found in inflammation and neoplasia [73, 74]. This enzyme is involved in the growth of angiogenesis, migration and invasion of tumor cells. MMP-9 clears collagen types IV, V, XI, and XVI which are important in cell invasion and metastasis [74].

High levels of MMP-9 expression are associated with a poor prognosis and advanced stage in several tumors including NPC [74-76]. Celecoxib, which is a COX-2 inhibitor, causes a decrease in MMP-9 expression in NPC cells in vitro. This is also in line with studies on pancreatic carcinoma cells [72, 73]. MMP-9 can be an important target in treating cancer [77].

3. CONCLUSION

CYP2E1 acts in the activation of pro-carcinogens such as nitrosamines and GSTs are involved in detoxifying carcinogens. The polymorphism of those enzyme increase the risk for NPC because of enhanced acitivity and diminished detoxification of carcinogen. Besides, protein expression in NPC tumor such as p38 MPAK, TNF-α, NF- κB, PPAR-gamma, LMP-1, VEGF, COX-2, and MMP-9 also affect the development and progression of cancer cells. Identification of risk factor and protein are help the clinician manage and prevent NPC.

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